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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,524	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,18-45 and 96-102* is/are pending in the application.

4a) Of the above claim(s) *14,15, 40-42,45 and 96-98* is/are withdrawn from consideration.

5)☒ Claim(s) *101 and 102* is/are allowed.

6)☒ Claim(s) *1-13,18-20,22-39,43,44 and 99* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 1/2/08 has been entered into the record. Claims 16-17 and 46-95 are cancelled. Claim 99-102 are added. Claims 1-15, 18-45 and 96-102 are pending. Claims 1-13, 18-39, 43-44 and 99-102 are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Elections/Restrictions

In response to Applicants request for the status of claims 12 and 13; claims 12 and 13 are under examination and were examined and rejected in the previous action. The examiner apologizes for any confusion that the office action summary, which both withdrew and rejected claims 12 and 13, may have caused.

Claim Objections

Claim 21 is objected to as being dependent on a rejected claim. See below.

Rejections Withdrawn

The rejection of claims 1,2,3 and 22-25 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendment to the claims.

The rejection of claims 1, 22-25 and 34-35 under 35 U.S.C. 102(e) as being anticipated by Olek et al. WO 2002/00926 A published Jan 3 2002 filed on June 29, 2001 is withdrawn in view of the amendment to the claim 1.

The rejection of claims 1, 3-13, 16-38 and 43 under 35 U.S.C. 103(a) as being unpatentable over Olek et al. WO 2002/00926 A. published Jan 3 2002 filed on June 29, 2001 in

view of Krieg et al. WO 2001/22972 A2, April 2001 is withdrawn in view of the amendment to the claim 1.

Rejections Maintained

The rejection of claims 39 and 44 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons made of record in the previous office action mailed 6/27/07.

Claim 39 is drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid is provided in an amount effective to treat or prevent an infectious disease and (claim 44) wherein the infectious disease is herpes simplex virus infection.

Applicants arguments and the response.

Applicant argues the Wands factors (*In re Wands*, 858 F.2d 731,737, 8USPQ.2d 1400, 1404 (Fed. Cir. 1988)) to provide support for enablement for the instant claims as follows:

Nature of the invention

Applicants state that the invention relates to nucleic acids that comprise a minimum a defined core of 21 nucleotide sequence (SEQ ID NO:1). Applicants state that the nucleic acids are immunostimulatory and are able to stimulate an innate immune response and adaptive immune response.

Breadth of the claims

Applicants state that the instant SEQ ID NO:1 is used to treat and prevent infectious disease, such as herpes simplex virus infection.

However, the Examiner disagrees with Applicants analysis of the breadth of the claims. The breadth and scope of infectious diseases that the claims contemplate to treat and prevent is extremely large. Applicants do not present the breadth of infectious diseases. As stated in the previous office action, the scope of infectious diseases includes a plethora of diseases caused by viruses, fungi, bacteria and parasites (Mechanisms of Microbial Diseases 3rd edition, edited by Moselio et al. 1999, p. XV-XVI).

State of the art and Predictability in the art.

Applicants state that at the time of filing the art was aware of immunostimulatory properties of a number of CpG nucleic acids. Applicants cite US patents 6,194,388 and 6,207,646 which disclose the use of CpG nucleic acids in the treatment and/or prevention of infectious disease including viral disease.

While, the examiner agrees that certain immunostimulatory CpG nucleic acids were known at the time of filing of the instant application, not one CpG nucleic acids has been shown to prevent all infectious diseases including herpes simplex virus infection. Further, the patents cited only contemplated the use of CpG nucleic acids but did not correlate immune response generated by CpG nucleic acids with prevention or treatment of the plethora of infectious diseases or disease caused by herpes simplex virus infection.

Applicants traverses Examiners characterization of the Choi et al and Gallichan et al references and argue that Choi et al does not test CpG nucleic acids alone and that the CpG nucleic acids of Gallicahn et al were not designed to test the efficacy of adjuvants when used alone.

The Examiner has carefully considered Applicants statements but disagree. Choi and Galician et al were cited because the art as of the time of filing taught that CpG DNA was used as adjuvant for antigenic vaccines against rotavirus and herpes simplex virus (Choi et al. Vaccine (2002) 20:1733-1740 and Gallichan et al. The Journal of Immunology (2001), 166 (5): 3451-3457). Choi and Gallichan was not cited for the analysis of the routes of administration of CpG nucleic acids but were cited to illustrate that CpG nucleic acids were used as adjuvants with rotavirus antigen or herpes simplex virus antigen.

Further, fig. 7 of Gallichan et al demonstrates that CpG when administered alone did not prevent or treat infection. Fig.7 of Gallichan et al show that when CpG immunostimulatory nucleic acid is administered to mice with antigen the HSV infectious titers reduces as compared to CpG alone wherein the infectious titers remains high. Thus, it cannot be concluded that CpG nucleic acids treats and prevents herpes simplex viral infection as the instant specification has not correlated the immune response generated by the instant CpG nucleic acid (SEQ ID NO:1) with reduction in herpes simplex virus infection as well as treatment or prevention of disease caused herpes simples virus infection.

Applicants argue that the Juffermans and Krieg et al reference stand for the proposition that CpG nucleic acids protect against M. tuberculosis and L. monocytogenes respectively.

Applicants' arguments have been carefully considered but are not persuasive. First, the claim 39 does not recite treat or prevent infection. Claim 39 recites treat or prevent infectious *disease*. The Krieg reference (Abstract presented at the 1996 meeting on Molecular Approaches to the Control of Infectious Diseases, Sept. 9-Sept. 13, 1996) teach reduction of infection (number of colonies in spleen and liver). The Krieg reference does not correlate reduction of infection with treatment of disease symptoms caused by L. monocytogenes. Also, the Krieg reference did not demonstrate prevention of infection as mice immunized with CpG still got infection, thus Krieg does not provide for prevention of disease caused by L. monocytogenes infection.

Second, the Juffermans reference show that CpG ODN reduced infection and did not correlate reduction of infection with treatment or prevention of tuberculosis disease caused by M. tuberculosis infection. Since the CpG treated mice were still infected (see fig. 1) the remaining infection can still cause Mycobacterial disease. Juffermans shows in fig.4 that mice treated twice with CpG ODN survived challenge with infection. However, the CpG ODN used in the Juffermans reference is not commensurate in scope with the instant CpG nucleic acid. Juffermans discloses a particular CpG nucleic acid which is different in structure from the claimed nucleic acid. As stated by Applicants under the nature of the invention, the instant invention relates to nucleic acids that comprise at a minimum a [particular] defined core 21 nucleotide sequence. This sequence is not disclosed by Juffermans et al. As the instant claims are drawn to a particular defined core sequence, one cannot extrapolate from the results of Juffermans unless the nucleic acid of Juffermans and that of the instant claims have the same core 21 nucleotide sequence structure.

As to the Gramzinski et al reference (Infection and Immunity, Mar. 2001, p. 1643-1649) the reference teaches that a CpG ODN induced protective immunity against sporozoite (of the rodent malaria parasite Plasmodium yoelli) challenge in mice. However, Gramzinski et al does not correlate the immune response generated by the particular CpG ODN used with treatment of a malaria disease such as cerebral malaria or anemia or jaundice caused by malaria infection or

correlate with treatment or prevention of malaria disease caused by the lethal human Plasmodium falciparum parasite and other Plasmodium species that infect humans and non-humans. Furthermore, similarly to Juffermans et al, the CpG ODN used by Gramzinski et al has a different structure compared to that of the instant claims which is not disclosed by Gramzinski et al. The CpG nucleic acid of Gramzinski et al does not share the core 21 nucleotide sequence of the instant SEQ ID NO: 1.

As to the Gura reference, the examiner acknowledges Applicants reference to MPEP 2164.01c where it states that "applicant need not demonstrate that the invention is completely safe".

In regards to the variability between CpG nucleic acids between host species and between cell types, Applicants argue that the claimed invention does not relate to any CpG nucleic acid, but rather a family of nucleic acids having at least 21 nucleotide consensus sequence (SEQ ID NO;1) to which immunostimulatory activity is attributed and that the instant Examples show that the claimed nucleic acids stimulate mouse and human immune cell including B and NK cells both of which are important in preventing and infectious disease. Applicants argue that Weiner et al discloses that CpG nucleic acids induce cytokines and activate immune cells with profiles similar to the instant nucleic acids and that Weiner teaches on p. 58 left column 4th paragraph that "solid animal model data suggest the shift of the immune response to a Th1 response by CpG ODN and could be of benefit for the treatment of infectious diseases or by serving as an immune adjuvant during vaccination". Applicants conclude that Weiner reference supports the predictability of immunostimulation using CpG nucleic acids in treating infectious diseases.

Applicants' arguments have been carefully considered but are not persuasive.

Weiner et al does not correlate the immune responses generated with CpG nucleic acids with treatment or prevention of any infectious disease or disease caused by herpes simplex virus e.g. herpes or herpes simplex virus infection. Further, Weiner et al does not teach that the instant core 21 nucleic acid sequence (SEQ ID NO: 1) wherein the C of at least one of the four CpG motifs is unmethylated, treats or prevents any infectious disease or herpes simplex virus infection. Weiner merely contemplates the use of CpG nucleic acids as immune adjuvants or for enhancing innate immunity and teach that these areas are under investigation. Infact, Weiner et al

teaches that all CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Ballas et al (J. Immunol. 2002, 168: 1212-1218) teaches that the selection of optimal CpG ODN, for example, in the case of cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

Since the instant claims are drawn to a particular CpG nucleic acid with a particular 21 core nucleic acid sequence, which is not disclosed by the above references, one cannot predict from studies with other particular CpG nucleic acids that the instant CpG nucleic acid will treat and prevent all infectious diseases and herpes simplex virus infection. For instance, Fig.7 of Gallichan et al show that when CpG immunostimulatory nucleic acid is administered to mice with antigen the HSV infectious titers reduces as compared to CpG alone wherein the infectious titers remains high. Gallichan et al teach in table 1 and fig. 7 that CpG ODN alone did not protect mice against infection when challenged with herpes simplex virus. Thus, the predictability of the instant CpG nucleic acid in treating or preventing infectious disease or herpes simplex virus infection cannot be predicted from the data of Gallichan.

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification. In the instant case, the art teaches that all CpG nucleic acids are not alike and that different effects are observed with different CpG nucleic acids (See Weiner, Ballas and Agrawal above) and Gallichan clearly teaches that one CpG nucleic acid when used alone did not treat or prevent herpes simplex virus infection.. Thus, for an unpredictable art such as treatment regiments using CpG oligonucleotides more guidance and a working example is needed.

Level of ordinary skill in the art and Amount of direction provided

Applicants' analysis of the level of ordinary skill in the art is acknowledged. As to the amount of direction provided, Applicants assert that the specification teaches how to make and use the claimed nucleic acids. This is carefully considered but not persuasive. Applicants have taught how to make the instant nucleic acid but have not taught how to use the nucleic acids as claimed i.e. to treat and prevention infectious diseases or herpes simplex virus infection. The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. As mentioned above, the art is unpredictable - all CpGs are not alike, different effects are observed with different CpG nucleic acids and Gallichan teach that a CpG nucleic nucleic acid administered alone did not prevent or treat herpes simplex viral infection. Thus, one of skill in the art could not predict the efficacy of the instant SEQ ID NO: 1 for the treatment of all infectious diseases.

Working examples

As to working examples, Applicant argue that the therapeutic efficacy of the claimed nucleic acid is attributable at least in part to their ability to stimulate Th1 biased immune responses and that the Examples demonstrate that the claimed nucleic acids are capable of priming the immune system even in the absence of antigen and that these are working examples as they correlate with the in vivo use of the nucleic acids. Applicants also argue that the examiner has not provided reasons for concluding a lack of correlation.

Applicants' arguments are carefully considered but are not persuasive.

Reasonable correlation must exist between the scope of the claims set forth herein and the disclosure in the specification.

The instant claims require that the claimed composition comprising the instant nucleic acid treat or prevent an infectious disease or herpes simplex virus infection. Although, the instant specification demonstrates that the instant nucleic acid induces an immune response, the specification is devoid of any correlation of the induced immune response with the treatment or prevention of any infectious disease or herpes simplex virus infection. The art is unpredictable - all CpGs are not alike, different effects are observed with different CpG nucleic acids and

Gallichan teach that a CpG nucleic acid did not prevent or treat herpes simplex viral infection. Thus, since the state of the art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification, a working example or a correlation commensurate with the scope of the claims i.e. to treat and prevent infectious disease or herpes simplex virus infection is needed. In the previous office action, the Examiner presented these reasons for coming to the conclusion of a lack of correlation.

Applicants question the relevance of the Chatterjee reference and argue that the instant use of the instant compositions are not limited to humans subjects and that effects with non-human subjects are commensurate with the scope of the claims; the therapy discussed by Chatterjee is idiotypic antibody cancer immunotherapy which is different from the instant claims.

Applicants' arguments are carefully considered but are not persuasive. The Chatterjee reference was cited to show that in vitro assays do not predict efficacy of in vivo treatment and it is well known for any therapy that after animal studies, studies are carried out to determine efficacy in human subjects. Further, as the scope of the claims also include treatment and prevention of infectious disease and herpes simplex virus infection in humans, correlation for the use of the instant composition to treat and prevention infectious disease and herpes simplex virus infection must exist, for humans. Correlation as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use (of the instant composition). An in vitro or in vivo animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples (see MPEP 2164.02). The instant specification does not set forth such a correlation between the induction of an immune response by the instant composition comprising the instant SEQ ID NO: 1 with treatment and prevention of infectious disease or herpes simplex virus infection in an animal model or in humans. The art is unpredictable - all CpGs are not alike, different effects are observed with different CpG nucleic acids and Gallichan teach that a CpG nucleic acid did not prevent or treat herpes simplex viral infection. Thus, a working example or correlation demonstrating the use of the instant composition as claimed is needed.

Quantity of Experimentation needed

Finally, Applicants conclude that in view of the teaching of the specification, the state and predictability in the art at the time of filing, the rejected claims can be practiced without undue experimentation.

Applicants' arguments are carefully considered but are not found persuasive.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing the factual considerations in *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole and one or more of these factors may weigh considerably more than the other in making the enablement rejection. In the instant case, the state of the art, the unpredictability of the art, the lack of working examples, the breadth of the claims weighed more in making the enablement rejection as set forth in the previous action and as set forth above. While the instant specification has taught how to make the instant invention, the specification has not taught how to use the invention as claimed i.e. to treat and prevent infectious diseases and herpes simplex virus infection.

New Rejection Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 18-20, 22-39, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Independent claim 1 now recites "wherein the C of at least one of the four CpG motifs is unmethylated". Applicants point to page 4 lines 11-13 and page 14 lines 1-10 for support for this amendment. Page 4 lines 11-13 do not teach that the C of at least one of the four CpG motifs is unmethylated. Page 4 lines 11-13 teaches phosphate back bone modifications and p. 14 lines 1-10 teach that the CpG motifs are preferably unmethylated. These pages of the specification do not teach the limitation that "at least one C of at least one of the four CpG motifs is unmethylated". P. 4 lines 18-20 teach that in one embodiment the immunostimulatory nucleic acid is free of unmethylated CpG and that in another embodiment the immunostimulatory nucleic acid includes at least 4 CpG motifs. This does not, however, provide support for the instant amended i.e. "at least one C … is unmethylated". Applicants can best resolve this issue by pointing to the specification by page and line number for where support exists for the instant amendment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 99 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is drawn to a composition comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, wherein the immunostimulatory nucleic acid is equal to or less than 100 nucleotides in length, and wherein the C of the four CpG motifs is unmethylated.

The metes and bounds of "less than 100 nucleotides in length" is not clear. If the immunostimulatory nucleic acid is less than 100 nucleotides in length can the immunostimulatory nucleic be less than the length of the nucleotide sequence of SEQ ID NO: 1?

Status of Claims

Claims 1-13, 18-20, 22-39, 43, 44 and 99 are rejected. Claim 21 is objected to. Claims 100-102 is allowable.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's Supervisor, Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/Patricia A. Duffy/
Primary Examiner, Art Unit 1645